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Associations of Total, Cognitive/Affective, and Somatic Depressive Symptoms and Antidepressant Use with Cardiovascular Disease-Relevant Biomarkers in HIV: Veterans Aging Cohort Study

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Abstract

Objective: We sought to determine associations of total, cognitive/affective, and somatic depressive symptoms and antidepressant use with biomarkers of processes implicated in cardiovascular disease in HIV (HIV-CVD).

Methods: We examined data from 1,546 HIV-positive and 843 HIV-negative veterans. Depressive symptoms were assessed using the Patient Health Questionnaire-9, and past-year antidepressant use was determined from VA pharmacy records. Monocyte (soluble CD14; sCD14), inflammatory (interleukin-6; IL-6), and coagulation (D-dimer) marker levels were determined from previously banked blood specimens. Linear regression models with multiple imputation were run to estimate associations between depression-related factors and CVD-relevant biomarkers.

Results: Among HIV-positive participants, greater somatic depressive symptoms were associated with higher sCD14 (exp[*b*]=1.02, 95% *CI:* 1.00-1.03) and D-dimer (exp[*b*]=1.06, 95% *CI:* 1.00-1.11) after adjustment for demographics and potential confounders. Further adjustment for antidepressant use and HIV factors slightly attenuated these relationships. Associations were also detected for antidepressant use, as selective serotonin reuptake inhibitor use was related to lower sCD14 (exp[*b*]=0.95, 95% *CI:* 0.91-1.00) and IL-6 (exp[*b*]=0.86, 95% *CI:* 0.76-0.96), and tricyclic antidepressant use was related to higher sCD14 (exp[*b*]=1.07, 95% *CI:* 1.03-1.12) and IL-6 (exp[*b*]=1.14, 95% *CI:* 1.02-1.28). Among HIV-negative participants, total, cognitive/affective, and somatic depressive symptoms were associated with higher IL-6, and tricyclic antidepressant use was related to higher sCD14.

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Conclusions: Our novel findings suggest that (a) monocyte activation and altered coagulation may represent two pathways through which depression increases HIV-CVD risk and that (b) tricyclic antidepressants may elevate and selective serotonin reuptake inhibitors may attenuate HIV-CVD risk by influencing monocyte and inflammatory activation.

Keywords: HIV, depression, somatic symptoms, soluble CD14, interleukin-6, D-dimer

Acronyms: ART = antiretroviral therapy; AUDIT-C = Alcohol Use Disorders Identification Test; CI = confidence interval; CV = coefficients of variability; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; ICD-9 = International Classification of Diseases, Ninth Revision; IL-6 = interleukin-6; LDL = low-density lipoprotein; NNRTI = nonnucleoside reverse-transcriptase inhibitors; NRTI = nucleoside reverse-transcriptase inhibitors; PHQ-9 = Patient Health Questionnaire-9; PI = protease inhibitors; sCD14 = soluble CD14; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; VA = Veterans Affair; VACS = Veterans Aging Cohort Study.

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Introduction

Highly-effective antiretroviral therapy (ART) has changed human immunodeficiency virus (HIV) from a life-threatening disease to a chronic disease requiring life-long management. However, with this transformation has come new health concerns. Chief among them is the high morbidity and mortality due to cardiovascular disease in HIV (HIV-CVD) (1). HIV-positive adults, versus HIV-negative adults, have a two-fold greater risk of developing CVD (1), and this elevated risk is not fully explained by established CVD risk factors or HIV factors (2). These observations have stimulated a search for novel risk factors for HIV-CVD that could serve as targets of future CVD prevention efforts.

One such emerging risk factor for HIV-CVD is depression, which consists of cognitive, affective, and somatic symptoms. Depression is common in HIV – it has an estimated prevalence of 40-42%, although rates vary widely across studies (3). Furthermore, consistent with the substantial literature linking depression with future CVD in non-HIV samples (4), our group recently reported that depressive disorders are independently associated with incident acute myocardial infraction (5) and heart failure (6) in people with HIV.

While the mechanisms underlying the depression to HIV-CVD relationship have yet to be elucidated, immune activation, systemic inflammation, and altered coagulation are strong candidates. First, all three processes play prominent roles in current conceptual frameworks of the pathogenesis of HIV-CVD, with HIV-related immune activation and the consequent systemic inflammation and altered coagulation contributing to atherosclerosis and clinical CVD onset (7). One indicator of immune activation is soluble CD14 (sCD14), which is considered a nonspecific

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marker of monocyte activation (8) and an acute phase protein (9). Second, immune activation, inflammatory, and coagulation markers – including sCD14, interleukin-6 (IL-6), and D-dimer, respectively – have been linked with both subclinical and clinical CVD in people with HIV (10-12). To illustrate, in the Strategies for Management of Antiretroviral Therapy (SMART) study, each standard deviation (*SD*) increase in IL-6 and D-dimer was associated with a 39% and 40% increased risk of a CVD event, independent of CVD risk factors (13). Third, initial evidence suggests that, in HIV-positive adults, depression may be associated with elevated immune activation (14-19) and inflammatory (19-24) markers. Although these depression-biomarker studies report novel and potentially significant findings, they utilized small samples, did not include an HIV-negative group, had limited adjustment for potential confounders, and/or did not examine depressive symptom clusters or antidepressant medication use.

Accordingly, our objective was to determine the independent associations of total depressive symptoms, cognitive/affective and somatic symptom clusters, and antidepressant use (regardless of treatment indication) with monocyte activation (sCD14), inflammatory (IL-6), and coagulation (D-dimer) markers in people living with HIV. While we hypothesized that greater total depressive symptoms would be related to higher and antidepressant use would be related to lower biomarker levels, we did not have hypotheses regarding depressive symptom clusters or antidepressant classes due to the paucity of evidence in HIV. However, a growing literature of non-HIV studies suggests that the somatic symptom cluster is more consistently associated with inflammatory markers than are the other clusters (see (25) for recent review), and a meta-analysis of non-HIV studies indicates that treatment with selective serotonin reuptake inhibitors (SSRIs), but not with other antidepressant classes, may reduce inflammatory markers (26).

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Moreover, in the lone study examining depressive symptom subtypes and inflammatory markers in HIV, the group with severe/moderate somatic symptoms had elevated IL-6 (22). To achieve our objective, we examined data from the Biomarker Cohort of the Veterans Aging Cohort Study (VACS), which consists of 1,546 HIV-positive and 843 HIV-negative veterans. Inclusion of the HIV-negative group allowed us to assess whether HIV modifies associations between depression-related variables and CVD-relevant biomarkers.

Material and Methods

Participants

Data came from the VACS Biomarker Cohort – a subset of participants from the parent VACS-9 study. VACS-9 is a prospective, multisite, cohort study of HIV-positive veterans and age, sex, race/ethnicity, and clinical site-matched HIV-negative veterans from nine Veterans Affair (VA) medical centers across the U.S. (27). The Biomarker Cohort consists of a subset of VACS-9 participants (n = 2,389) who consented to provide a blood sample at one time point between 2005-2006 (28). The matching procedures were not reapplied to the Biomarker Cohort.

Measures

Depressive Symptoms. In the parent VACS-9 study, the Patient Health Questionnaire-9 (PHQ-9) (29) was administered multiple times to assess depressive symptoms over the last two weeks. The available studies suggest that the PHQ-9 is a reliable and valid instrument in people with HIV (30). For the present analysis, we used data from the PHQ-9 administration closest to the blood draw date (median [25^{th}-75^{th} percentile] = 31 [0-231] days prior to blood draw). PHQ-9 total scores range from 0-27, with ≥10 being indicative of clinically significant depressive

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symptoms (31). In addition to the total score (sum of all nine items), we computed the cognitive/affective score as the sum of items 1 (anhedonia), 2 (depressed mood), 6 (low self-esteem), 7 (concentration problems), 8 (psychomotor retardation/agitation), and 9 (suicidal ideation) and the somatic score as the sum of items 3 (sleep disturbance), 4 (fatigue), and 5 (appetite changes). The PHQ-9 has high internal consistency and good sensitivity and specificity for identifying cases of major depressive disorder (29, 31). The cognitive/affective and somatic symptom clusters have been validated across major sociodemographic groups in a recent study utilizing a large, nationally representative sample of U.S. adults (32). For participants who were missing data for one item (n=147), we imputed that value with the mean of the other eight items. The PHQ-9 scores were converted to z-scores prior to analysis so that a 1-unit change corresponded to a 1-*SD* change.

Antidepressant Use. Antidepressant use was defined as documentation of a filled prescription for an antidepressant medication up to 365 days before the blood draw date in the VA pharmacy records data. Separate yes/no variables were computed for following antidepressant classes: selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA), and miscellaneous other antidepressant. Medications from the following classes were coded as miscellaneous other: monoamine oxidase inhibitor, serotonin-norepinephrine reuptake inhibitor, serotonin antagonist and reuptake inhibitor, norepinephrine reuptake inhibitor, norepinephrine-dopamine reuptake inhibitor, and tetracyclic antidepressant. The treatment indication for the detected antidepressant use is not known. Of note, the indication for SSRIs and certain medications in our miscellaneous category (e.g., serotonin-norepinephrine reuptake

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inhibitors) is often a depressive disorder, whereas the indication for TCAs and other medications in our miscellaneous category (e.g., trazodone) is often insomnia or pain conditions (33).

Monocyte Activation, Inflammatory, and Coagulation Markers. As is described elsewhere (28, 34), blood samples were collected at one time point between 2005-2006 using serum separator and EDTA tubes and were shipped to a central repository at the Massachusetts Veterans Epidemiology Research and Information Center. Assays for biomarkers examined here were conducted at the Laboratory for Clinical Biochemistry Research at the University of Vermont and used four controls per sample to assess interassay coefficients of variability (CVs). sCD14 was quantified by an enzyme-linked immunosorbent assay (Quantikine sCD14 Immunoassay, R&D Systems, Minneapolis, MN) with a detectable range of 40-3,200 ng/ml. The interassay CVs ranged from 7.2-8.1%. IL-6 was quantified by a chemiluminescent immunoassay (QuantiGlo IL-6 immunoassay, R&D Systems, Minneapolis, MN) with detectable range of 0.4-10,000 pg/mL. The interassay CVs ranged from 7.7-12.3%. D-dimer was quantified by a STAR automated coagulation analyzer (Diagnostica Stago, Parsippany, NJ) using an immunoturbidometric assay (Liatest D-DI) with a detectable range of 0.01-20 ug/mL. The interassay CVs ranged from 2.8-14.8%. All three biomarkers were natural log transformed before analysis to approximate a normal distribution.

Covariates. As in our past work (28), covariate data were obtained closest to the blood draw date (see Table 1 for the coding of variables). Demographic factors were age, sex, and race/ethnicity. Several biomedical and behavioral factors were included in our models as covariates. CVD was identified by an *International Classification of Diseases, Ninth Revision*

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(ICD-9) code for acute myocardial infarction, unstable angina, cardiovascular revascularization, ischemic stroke, hemorrhagic stroke, heart failure, or cardiomyopathy before the blood draw date. Diabetes was defined by a previously validated metric using glucose values, diabetes medication use, and/or at least one inpatient or two outpatient ICD-9 codes for diabetes (35). Blood pressure was computed as the average of the three routine outpatient measurements obtained closest to the blood draw date. Hypertension was identified by blood pressure ≥140/90 mmHg or documentation of antihypertensive medication. Low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were obtained from the VA Corporate Data Warehouse. Statin use was defined by a filled prescription receipt for a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor. Hepatitis C infection was identified by a positive hepatitis C virus antibody test or at least one inpatient or two outpatient ICD-9 codes for hepatitis C infection. Estimated glomerular filtration rate (eGFR; a renal function indicator) and hemoglobin were defined by laboratory values extracted from the VA Corporate Data Warehouse. Body mass index and smoking were determined from the VA Health Factors dataset (36). The Alcohol Use Disorders Identification Test (AUDIT-C) (37) and alcohol abuse/dependence ICD-9 codes were used to create a 4-level alcohol use variable: not current, not hazardous (AUDIT-C <4), hazardous or heavy episodic (AUDIT-C ≥4), abuse/dependence (ICD-9 code). Cocaine abuse/dependence was identified by an ICD-9 code for a cocaine use disorder before the blood draw date. We included these substance use variables, as they have been associated with both depression and the biomarkers (28, 38, 39) and, thus, could confound the associations of interest.

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HIV factors were $CD4^+$ T-cell count, HIV-1 RNA level, and ART use. $CD4^+$ T-cell count and HIV-1 RNA level, measured as part of routine clinical care, were determined from VA Corporate Data Warehouse data obtained closest to the blood draw date (up to 180 days after). ART use was determined from VA pharmacy data for the timeframe 180 days prior to 7 days after the blood draw date and included the following classes: nucleoside reverse-transcriptase inhibitors (NRTI), nonnucleoside reverse-transcriptase inhibitors (NNRTI), and protease inhibitors (PI).

Data Analysis

Participant characteristics were stratified by depression status separately for veterans with and without HIV (see Table 1). Independent samples *t* tests or Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables were used to assess for differences in participant characteristics by depression status. For these tests, the biomarker variables were examined in their original scale.

Linear regression models were run to estimate the associations of total, cognitive/affective, and somatic depressive symptoms and antidepressant use with monocyte activation, inflammatory, and coagulation markers separately in veterans with and without HIV. Multiple imputations with five imputed datasets were generated using the "mi impute chained" command in Stata. Models were fitted in each imputed dataset and combined using Rubin's rule to obtain pooled regression coefficients and standard errors.

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For each outcome variable (log transformed sCD14, IL-6, and D-dimer), we constructed four models. Model 1 adjusted for demographics (age, sex, and race/ethnicity). Model 2 was our primary model and further adjusted for the following biomedical and behavioral factors that could confound associations between depression-related variables and the biomarkers: CVD, diabetes, hypertension, LDL cholesterol, HDL cholesterol, triglycerides, statin use, hepatitis C infection, renal function, hemoglobin, BMI, smoking, alcohol use, and cocaine abuse/dependence. Model 3 added the three antidepressant use variables (past-year SSRI, TCA, and other antidepressant use) to Model 2. Model 4 added the HIV factors ($CD4^+$ T-cell count, HIV-1 RNA level, and ART use) to Model 3. Separate models were run for each PHQ-9 variable (*z*-scored total, cognitive/affective, and somatic scores). Models 1-3 were also run in HIV-negative veterans. Finally, the HIV x PHQ-9 total score, HIV x PHQ-9 cognitive/affective score, and HIV x PHQ-9 somatic score interactions were tested separately in Model 2's that included the HIV main effect and involved entire cohort. Similarly, the HIV x SSRI use, HIV x TCA use, HIV x other antidepressant use interactions were tested simultaneously in a Model 3 that included the HIV main effect and involved entire cohort.

Because our outcome variables were log transformed, we present the exponentiated regression coefficient [exp(b)] and its 95% confidence interval (CI) for each association. For continuous *z*-scored exposure variables (PHQ-9 variables), we computed the percent change in each biomarker per one-unit (i.e., 1-*SD*) change in each PHQ-9 variable using the following equation: [exp(b) – 1] x 100. For dichotomous exposure variables (antidepressant use variables), we used the same equation to compute the percent change in each biomarker per one-unit change (i.e., switching from "no" to "yes") in each antidepressant use variable.

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Results

Characteristics of Veterans in the VACS Biomarker Cohort

Table 1 presents descriptive statistics for the biomarkers, depression variables, and covariates stratified by depression status (PHQ-9 total score ≥10: depressed, <10: not depressed,) separately for veterans with and without HIV. Of note, the *SD*s for the PHQ-9 total, cognitive/affective, and somatic scores were 6.6, 4.3, and 2.7 for the HIV-positive participants and 7.1, 4.7, and 2.9 for the HIV-negative participants.

Among the HIV-positive participants, sCD14 was higher in the depressed group, but significant group differences were not detected for IL-6 or D-dimer. As was expected, the PHQ-9 scores and antidepressant use rates were all higher in the depressed group. Significant differences in covariates were also observed, with the depressed group having higher levels/rates for hepatitis C infection, smoking, alcohol use, cocaine abuse/dependence, and HIV-1 RNA and lower levels/rates for age, LDL cholesterol, statin use, and $CD4^+$ T-cell count.

Among the HIV-negative participants, IL-6 and all depression variables were higher in the depressed group. Significant group differences were not detected for sCD14 or D-dimer. The depressed group had higher levels/rates for diabetes, triglycerides, hepatitis C infection, smoking, and cocaine abuse/dependence and lower levels/rates for age and statin use.

Depressive Symptoms, Antidepressant Use, and Monocyte Activation

Among the HIV-positive participants (see Table 2), the PHQ-9 total, cognitive/affective, and somatic scores were all associated with higher sCD14 in Model 1 adjusting for demographic

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factors. The somatic score remained positively related to sCD14 in our primary model (Model 2) adjusting for several potential confounders, although the total and cognitive/affective scores did not. The exp(*b*) of 1.02 indicates that every 1-*SD* increase in the somatic score (2.7 points on a 0-9 scale) was associated with a 2% increase in sCD14 on average [(1.02 – 1) x 100]. Model 3, which added the antidepressant use variables, revealed that SSRI use was negatively related and TCA use was positively related to sCD14. SSRI use (versus no use) was associated with a 5% decrease in sCD14 on average, whereas TCA use was associated with a 7% increase in sCD14 on average. The somatic score remained positively related to sCD14 in Model 3. In Model 4 further adjusting for HIV factors, the pattern of results was similar, although the associations for the somatic score and SSRI use were slightly attenuated.

Among the HIV-negative participants (see Table 2), the PHQ-9 scores were not associated with sCD14 in Models 1 or 2. Model 3 showed that TCA use was positively related to sCD14, with TCA use being associated with a 6% increase in sCD14 on average. The total and cognitive/affective scores were negatively related to sCD14 in Model 3; however, these associations may be unreliable, as they were not observed in Models 1 or 2.

The HIV x SSRI use interaction was significant (p = 0.023), indicating that the relationship between SSRI use and sCD14 was stronger among the HIV-positive (negative association) versus the HIV-negative (no association) participants. The interactions between HIV and PHQ-9 total score, cognitive/affective score, somatic score, TCA use, and other antidepressant use were not significant (all ps >0.18), demonstrating that these relationships did not differ by HIV status.

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Depressive Symptoms, Antidepressant Use, and Systemic Inflammation

Among the HIV-positive participants (see Table 3), the PHQ-9 total and cognitive/affective scores were not related to IL-6 in Models 1 or 2. Although the somatic score was associated with higher IL-6 in Model 1, adjustment for potential confounders in Model 2 eliminated this relationship. Model 3 revealed that SSRI use was associated with 14% decrease and TCA use was associated with 14% increase in IL-6 on average. Model 4 results were similar to those of Model 3.

Among the HIV-negative participants (see Table 3), the PHQ-9 total, cognitive/affective, and somatic scores were all associated with higher IL-6 in Models 1 and 2. In Model 2, every 1-*SD* increase in the PHQ-9 total (7.1 points on a 0-27 scale), cognitive/affective (4.7 points on a 0-18 scale), and somatic score (2.9 points on a 0-9 scale) was associated with a 8%, 7%, and 9% increase in IL-6 on average, respectively. In Model 3, the somatic score remained positively related to IL-6, although no antidepressant use variable was associated with IL-6.

The interactions between HIV and PHQ-9 total score ($p = 0.013$), cognitive/affective score ($p = 0.015$), somatic score ($p = 0.025$), and SSRI use ($p = 0.005$) were significant. These results indicate that (a) relationships between the PHQ-9 scores and IL-6 were stronger among the HIV-negative (positive associations) versus the HIV-positive (no associations) participants and that (b) the relationship between SSRI use and IL-6 was stronger among the HIV-positive (negative association) versus the HIV-negative (no association) participants. The HIV x TCA use and HIV x other antidepressant use interactions were not significant (both *p*s >0.41).

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Depressive Symptoms, Antidepressant Use, and Altered Coagulation

Among the HIV-positive participants (see Table 4), the PHQ-9 total, cognitive/affective, and somatic scores were all associated with higher D-dimer in Model 1. However, only the relationship with the somatic score remained significant in Model 2, with every 1-*SD* increase in that score (2.7 points on a 0-9 scale) being associated with a 6% increase in D-dimer on average. In Model 3, no antidepressant use variable was associated with D-dimer. The association for the PHQ-9 somatic score was slightly attenuated in Models 3 and 4, falling short of significance.

Among the HIV-negative participants (see Table 4), no PHQ-9 score or antidepressant use variable was associated with D-dimer across models.

The interactions between HIV and PHQ-9 total score, cognitive/affective score, somatic score, SSRI use, TCA use, and other antidepressant use were all not significant (all *p*s >0.15).

Discussion

We report novel independent associations between depression-related variables and monocyte activation, systemic inflammation, and altered coagulation – which are all implicated in HIV-CVD (7). In HIV-positive veterans, greater somatic depressive symptoms were related to higher sCD14 and D-dimer in our primary model adjusting for demographics and potential medical and behavioral confounders. Further adjustment for antidepressant use and HIV factors slightly attenuated these relationships. In addition, past-year SSRI use was linked to lower and past-year TCA use was linked to higher sCD14 and IL-6 in HIV-positive veterans.

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The observed relationships are small (2%-14% biomarker change), and their clinical relevance is unclear. Nevertheless, because we found relationships unlikely due to chance, our results raise the possibilities that (a) monocyte activation and altered coagulation may be two of the likely many mechanisms through which depressive symptoms may increase HIV-CVD risk and that (b) TCA treatment may elevate and SSRI treatment may attenuate HIV-CVD risk due to their possible effects on monocyte activation and systemic inflammation. Future prospective studies, ideally randomized controlled trials, are needed to rigorously evaluate these possibilities.

Our study makes important contributions to the HIV literature examining relationships between depression-related factors and CVD-relevant biomarkers, as it has the largest sample to date, included an HIV-negative group, adjusted for several potential confounders, and examined depressive symptoms clusters and antidepressant use. HIV studies (14-19) have detected depression-immune activation associations, as we did here for sCD14. We extend those findings with evidence that the somatic symptoms may be contributing more to this link than the cognitive/affective symptoms. HIV studies have also reported depression-inflammation associations (19-24), conflicting with the lack of relationships for IL-6 here. Of relevance, Norcini Pala and colleagues (22) examined depressive symptom subtypes, observing elevated IL-6 in the group with severe/moderate somatic symptoms. A possible explanation for these discrepant results is that our models included more extensive adjustment for potential confounders than most studies. Consistent with this idea, greater somatic symptoms were associated with higher IL-6 in our demographics-adjusted model but not in our subsequent models. To our knowledge, our study is the first to report a relationship between greater depressive

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symptoms and higher levels of a coagulation marker (D-dimer) in HIV. Our findings further suggest that this is another link to which the somatic symptoms may be contributing more than the cognitive/affective symptoms.

There are five plausible, non-mutually exclusive explanations for the relationships we observed. One, elevated depressive symptoms could lead to immune activation and altered coagulation through the putative mechanisms underlying depression-immune function relationships, such as autonomic dysfunction, hypothalamic-pituitary-adrenal axis dysregulation, and increased adiposity (40, 41). In line with our stronger associations of the somatic cluster with sCD14 and D-dimer, others have found the somatic depressive symptoms to be more strongly related to autonomic dysfunction (42) and abdominal obesity (43) than the cognitive depressive symptoms. Two, depression has been associated with markers of increased gut permeability (44, 45), which promotes immune activation due to increased microbial translocation from the gut to circulation (46). Three, a candidate behavioral mechanism specific to HIV is ART nonadherence, as depression is associated with poorer adherence to HIV treatment (47), with resulting poorer control of viremia-associated immune activation. Four, increased release of proinflammatory cytokines in the central nervous system – due, in part, to HIV-related immune activation – could produce elevated depressive symptoms, particularly the somatic symptoms ("sickness behavior"), via their effects on neurobiological systems implicated in depression (48-50). Five, confounders, such as HIV severity, could be contributing to the observed relationship, especially considering the overlap between somatic depressive symptoms and HIV symptoms (51). However, our primary models adjusted for several comorbid conditions, and further adjustment for viral load and $CD4^+$ T-cell count only slightly attenuated associations.

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Although we are not aware of previous HIV studies examining relationships between antidepressant use and CVD-relevant biomarkers, meta-analytic evidence from non-HIV studies indicates that IL-6 decreases following SSRI, but not TCA, treatment (26). Furthermore, a systematic review of non-HIV studies concluded that both SSRIs and TCAs appear to reduce inflammatory markers (52). Those prior reviews are consistent with our finding that SSRI use is associated with lower immune activation (sCD14) and systemic inflammation (IL-6) in people with HIV. SSRIs may have direct immunomodulary effects or indirect effects through improved depression and HIV treatment adherence (53, 54). SSRIs may also have antimicrobial effects and, thus, may restore gut microbiota balance (55), thereby decreasing gut permeability and the consequent bacterial translocation, immune activation, and systemic inflammation. Those prior reviews, however, are inconsistent with our finding that TCA use is related to higher sCD14 and IL-6 levels. One possible explanation for this discrepancy is that TCA use is acting as a marker of treatment-resistant depression, as SSRIs are typically recommended as first-line antidepressants (56). Another possible explanation is that TCA use is acting as a proxy for conditions not in our models, as these medications are often prescribed for other conditions linked with immune/inflammatory activation, such as insomnia and chronic pain (33).

We also observed noteworthy associations in HIV-negative veterans. First, we detected positive associations of total, cognitive/affective, and somatic depressive symptoms with IL-6. Second, we found that TCA use was linked to higher sCD14. Our findings are in line with a recent meta-analysis of non-HIV studies showing that depression is associated with higher inflammatory markers predictive of CVD (57). We also detected some differences in relationships by HIV status. SSRI use was more strongly associated with lower sCD14 and IL-6

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in HIV-positive veterans, raising the possibility that SSRI therapy (currently first-line antidepressants) may be a promising approach to reducing monocyte and inflammatory activation in depressed people with HIV. In addition, PHQ-9 scores were more strongly related to higher IL-6 in HIV-negative veterans.

Some limitations deserve attention. First, our cross-sectional data prevents us from drawing inferences regarding directionality of associations, and both directions are plausible. More specifically, because the immune activation, inflammatory, and coagulation markers were assessed at only one time point in the VACS Biomarker Cohort, we could not examine associations between baseline depression variables and changes over time in these biomarkers. Second, our yes/no past-year antidepressant use variables lack precision, which could have led us to underestimate their true effect sizes. Incorporating dose, duration, and recency of use would provide a more nuanced assessment. In addition, we do not know the treatment indication for the detected antidepressant use. To illustrate, 28% of HIV-positive and HIV-negative veterans classified as not depressed had past-year antidepressant use – a group that likely consists of those whose prior depression had been successfully treated and those taking antidepressants for other indications, such as anxiety, insomnia, or pain conditions (33). Third, it is unknown whether our findings extend to women. The VACS Biomarker Cohort, especially the HIV-positive group, contains a low percentage of women, which may explain the observed lower prevalence of depression (23%) in veterans with HIV compared to prior estimates (3).

In sum, our findings suggest that (a) monocyte activation and altered coagulation may be two pathways through which depression increases HIV-CVD risk and that (b) TCAs may elevate

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and SSRIs may attenuate HIV-CVD risk by influencing monocyte activation and systemic inflammation. Ultimately, elucidating the mechanisms underlying the depression to HIV-CVD association could identify additional targets (beyond depression itself) for novel HIV-CVD prevention efforts. Moreover, determining the effect of various classes of antidepressants on HIV-CVD risk and relevant biomarkers could lead to the development of antidepressant algorithms to simultaneously treat depression and lower CVD risk in people with HIV.

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Table 1. Characteristics of Veterans in the VACS Biomarker Cohort by HIV Status and Depression Status

	HIV-Positive (*n*=1,527)			HIV-Negative (*n*=837)		
	Depressed (*n*=348)	**Not Depressed (*n*=1,179)**	***p***	**Depressed (*n*=263)**	**Not Depressed (*n*=574)**	***p***
Biomarkers						
Soluble CD14, median (25^{th}-75^{th} percentile), ng/mL	1822 (1511-2137)	1694 (1432-2073)	0.002	1757 (1491-2075)	1720 (1467-2032)	0.44
Interleukin-6, median (25^{th}-75^{th} percentile), pg/mL	2.20 (1.47-3.55)	2.03 (1.41-3.35)	0.14	2.10 (1.25-3.51)	1.73 (1.13-2.90)	0.013
D-dimer, median (25^{th}-75^{th} percentile), μg/mL	0.29 (0.16-0.53)	0.26 (0.15-0.48)	0.091	0.32 (0.21-0.53)	0.29 (0.21-0.53)	0.80
Depression Variables						
PHQ-9 Total Score (0-27), mean (*SD*)	15.9 (5.2)	2.7 (2.9)	<0.001	16.1 (4.9)	2.9 (2.9)	<0.001
PHQ-9 Cognitive/affective Score (0-18), mean (*SD*)	9.6 (4.1)	1.2 (1.8)	<0.001	9.8 (3.7)	1.4 (1.8)	<0.001
PHQ-9 Somatic Score (0-9), mean (*SD*)	6.3 (2.1)	1.4 (1.6)	<0.001	6.4 (2.1)	1.5 (1.6)	<0.001
Past-Year SSRI Use, *n* (%)	180 (52)	248 (21)	<0.001	141 (54)	121 (21)	<0.001
Past-Year TCA Use, *n* (%)	82 (24)	139 (12)	<0.001	69 (26)	64 (11)	<0.001
Past-Year Other Antidepressant Use, *n* (%)	162 (47)	227 (19)	<0.001	138 (52)	122 (21)	<0.001
Covariates						
Age, mean (*SD*), years	51.1 (7.6)	51.9 (8.4)	<0.001	52.0 (7.9)	54.2 (9.8)	<0.001
Women, *n* (%)	10 (3)	32 (3)	0.87	32 (12)	49 (9)	0.10
Race/Ethnicity, *n* (%)			0.22			0.25
White	77 (22)	213 (18)		56 (21)	117 (20)	
African American	224 (64)	824 (70)		167 (64)	395 (69)	
Hispanic	31 (9)	101 (9)		28 (11)	40 (7)	
Other	16 (5)	41 (3)		12 (5)	22 (4)	
Cardiovascular Disease, *n* (%)	75 (22)	204 (17)	0.071	72 (27)	158 (28)	0.96
Diabetes, *n* (%)	67 (19)	234 (20)	0.81	93 (35)	154 (27)	0.012
Hypertension, *n* (%)	90 (26)	272 (23)	0.29	72 (27)	157 (27)	0.97
LDL Cholesterol, *n* (%)			0.014			0.24
<100 mg/dL	198 (57)	587 (50)		138 (52)	261 (45)	
100-129 mg/dL	98 (28)	330 (28)		67 (25)	170 (30)	
130-159 mg/dL	29 (8)	168 (14)		31 (12)	79 (14)	
≥160 mg/dL	14 (4)	60 (5)		15 (6)	42 (7)	

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HDL Cholesterol, *n* (%)			0.71			0.17
≥60 mg/dL	51 (15)	175 (15)		50 (19)	87 (15)	
40-59 mg/dL	134 (39)	475 (40)		112 (43)	281 (49)	
<40 mg/dL	156 (45)	496 (42)		92 (35)	186 (32)	
Triglycerides ≥150 mg/dL, *n* (%)	170 (49)	513 (44)	0.078	91 (35)	157 (28)	0.035
Statin Use, *n* (%)	79 (23)	376 (32)	0.001	100 (38)	257 (45)	0.067
Hepatitis C Infection, *n* (%)	209 (60)	510 (43)	<0.001	98 (37)	164 (29)	0.012
eGFR <60 ml/min/1.73 m^2, *n* (%)	58 (10)	18 (7)	0.45	92 (8)	23 (7)	0.13
Hemoglobin, *n* (%)			0.92			0.73
≥14 g/dL	179 (51)	602 (51)		140 (53)	317 (55)	
12.0-13.9 g/dL	130 (37)	433 (37)		106 (40)	217 (38)	
<12 g/dL	39 (11)	141 (12)		16 (6)	40 (7)	
Body Mass Index ≥30 kg/m^2, *n* (%)	61 (18)	185 (16)	0.44	123 (47)	265 (46)	0.85
Smoking, *n* (%)			<0.001			0.001
Never	67 (19)	300 (25)		51 (19)	146 (25)	
Past	70 (20)	326 (28)		63 (24)	181 (32)	
Current	211 (61)	553 (47)		149 (57)	245 (43)	
Alcohol Use, *n* (%)			<0.001			0.092
Not Current	104 (30)	418 (35)		99 (38)	214 (37)	
Not Hazardous	66 (19)	284 (24)		36 (14)	107 (19)	
Hazardous or Heavy Episodic	45 (13)	194 (16)		33 (13)	87 (15)	
Abuse/Dependence	132 (38)	279 (24)		95 (36)	166 (29)	
Cocaine Abuse/Dependence, *n* (%)	165 (47)	386 (33)	<0.001	120 (46)	197 (34)	0.002
CD4+ T-cell Count, *n* (%)			0.002	---	---	---
≥500/mm^3	100 (29)	432 (37)				
200-499/mm^3	163 (47)	539 (46)				
<200/mm^3	85 (24)	204 (17)				
HIV-1 RNA Level ≥500 copies/mL, *n* (%)	150 (43)	366 (31)	<0.001	---	---	---
Antiretroviral Therapy Use, *n* (%)	292 (84)	1004 (85)	0.57	---	---	---

Note. PHQ-9 total score ≥10: depressed, <10: not depressed. All variables had complete data except (*n*): IL-6 (2,342), sCD14 (2,354), D-dimer (2,349), PHQ-9 total score (2,364), PHQ-9 cognitive/affective score (2,325), PHQ-9 somatic score (2,296), hypertension (2,385), LDL cholesterol (2,311), HDL cholesterol (2,319), triglycerides (2,349), eGFR (2,380), hemoglobin (2,385), body mass index (2,380), smoking (2,385), alcohol use (2,384), CD4+ T-cell count (1,542), and HIV-1 RNA level (1,542). HIV = human immunodeficiency virus. VACS = Veterans Aging Cohort Study. PHQ-9 = Patient Health Questionnaire-9. SSRI = selective serotonin reuptake inhibitor. TCA = tricyclic antidepressant. LDL = low-density lipoprotein. HDL = high-density lipoprotein. eGFR = estimated glomerular filtration rate. RNA = ribonucleic acid.

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Table 2. Linear Regression Models Examining Associations of Depressive Symptoms and Antidepressant Use with Soluble CD14 Separately among HIV-Positive and HIV-Negative Veterans in the VACS Biomarker Cohort

	HIV-Positive (*n*=1,546)							
	Model 1: Demographics-Adjusted Model[a]		**Model 2 (Primary Model): Model 1 + Confounders[b]**		**Model 3: Model 2 + Antidepressants**		**Model 4: Model 3 + HIV Factors[c]**	
	exp(*b*)	**95% *CI***	**exp(*b*)**	**95% *CI***	**exp(*b*)**	**95% *CI***	**exp(*b*)**	**95% *CI***
PHQ-9 Total	**1.02***	1.01-1.04	1.01†	1.00-1.03	1.01	1.00-1.03	1.01	0.99-1.02
PHQ-9 Cognitive/affective	**1.02***	1.00-1.03	1.01	0.99-1.02	1.01	0.99-1.02	1.00	0.99-1.02
PHQ-9 Somatic	**1.03***	1.01-1.04	**1.02***	1.00-1.03	**1.02***	1.00-1.03	1.01†	1.00-1.03
SSRI Use					**0.95***	0.91-1.00	**0.96***	0.92-1.00
TCA Use					**1.07***	1.03-1.12	**1.07***	1.02-1.11
Other Antidepressant Use					1.04†	1.00-1.09	1.04†	1.00-1.09
	HIV-Negative (*n*=843)							
PHQ-9 Total	1.01	0.99-1.02	0.99	0.98-1.01	**0.98***	0.96-1.00		
PHQ-9 Cognitive/affective	1.00	0.99-1.02	0.99	0.97-1.01	**0.98***	0.96-1.00		
PHQ-9 Somatic	1.01	0.99-1.03	1.00	0.98-1.01	0.99	0.97-1.00		
SSRI Use					1.04†	0.99-1.10		
TCA Use					**1.06***	1.00-1.11		
Other Antidepressant Use					1.01	0.96-1.07		

Note. Soluble CD14 is log transformed. PHQ-9 variables are *z* scored. Statistically significant effects are bolded. HIV = human immunodeficiency virus. VACS = Veterans Aging Cohort Study. exp(b) = exponentiated regression coefficient. CI = confidence interval. PHQ-9 = Patient Health Questionnaire-9. SSRI = selective serotonin reuptake inhibitor. TCA = tricyclic antidepressant.

[a]Adjusted for age, sex, and race/ethnicity.

[b]Additionally adjusted for cardiovascular disease, diabetes, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, statin use, hepatitis C infection, renal function, hemoglobin, BMI, smoking, alcohol use, and cocaine abuse/dependence.

[c]Additionally adjusted for CD4+ T-cell count, HIV-1 RNA level, and ART use.

*$p < .05$

†$p = .05$-$.10$

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Table 3. Linear Regression Models Examining Associations of Depressive Symptoms and Antidepressant Use with Interleukin-6 Separately among HIV-Positive and HIV-Negative Veterans in the VACS Biomarker Cohort

	HIV-Positive (*n*=1,546)							
	Model 1: Demographics-Adjusted Model[a]		**Model 2 (Primary Model): Model 1 + Confounders[b]**		**Model 3: Model 2 + Antidepressants**		**Model 4: Model 3 + HIV Factors[c]**	
	exp(*b*)	**95% *CI***	**exp(*b*)**	**95% *CI***	**exp(*b*)**	**95% *CI***	**exp(*b*)**	**95% *CI***
PHQ-9 Total	1.04†	1.00-1.08	1.00	0.96-1.04	1.00	0.96-1.04	0.99	0.95-1.02
PHQ-9 Cognitive/affective	1.03	0.99-1.07	0.99	0.95-1.03	0.99	0.95-1.03	0.97	0.94-1.01
PHQ-9 Somatic	**1.06***	1.02-1.10	1.01	0.98-1.05	1.02	0.98-1.06	1.01	0.97-1.05
SSRI Use					**0.86***	0.76-0.96	**0.86***	0.77-0.96
TCA Use					**1.14***	1.02-1.28	**1.13***	1.01-1.27
Other Antidepressant Use					1.12†	0.99-1.26	1.13†	1.00-1.27
	HIV-Negative (*n*=843)							
PHQ-9 Total	**1.11***	1.05-1.18	**1.08***	1.02-1.14	1.05†	0.99-1.12		
PHQ-9 Cognitive/affective	**1.10***	1.04-1.16	**1.07***	1.01-1.13	1.04	0.98-1.10		
PHQ-9 Somatic	**1.13***	1.06-1.19	**1.09***	1.03-1.15	**1.06***	1.00-1.12		
SSRI Use					1.12	0.94-1.33		
TCA Use					1.05	0.88-1.24		
Other Antidepressant Use					1.07	0.90-1.27		

Note. Interleukin-6 is log transformed. PHQ-9 variables are *z* scored. Statistically significant effects are bolded. HIV = human immunodeficiency virus. VACS = Veterans Aging Cohort Study. exp(b) = exponentiated regression coefficient. CI = confidence interval. PHQ-9 = Patient Health Questionnaire-9. SSRI = selective serotonin reuptake inhibitor. TCA = tricyclic antidepressant.

[a]Adjusted for age, sex, and race/ethnicity.

[b]Additionally adjusted for cardiovascular disease, diabetes, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, statin use, hepatitis C infection, renal function, hemoglobin, BMI, smoking, alcohol use, and cocaine abuse/dependence.

[c]Additionally adjusted for CD4+ T-cell count, HIV-1 RNA level, and ART use.

*$p < .05$

†$p = .05$-$.10$

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Table 4. Linear Regression Models Examining Associations of Depressive Symptoms and Antidepressant Use with D-Dimer Separately among HIV-Positive and HIV-Negative Veterans in the VACS Biomarker Cohort

	HIV-Positive (*n*=1,546)							
	Model 1: Demographics-Adjusted Model[a]		**Model 2 (Primary Model): Model 1 + Confounders[b]**		**Model 3: Model 2 + Antidepressants**		**Model 4: Model 3 + HIV Factors[c]**	
	exp(*b*)	**95% *CI***	**exp(*b*)**	**95% *CI***	**exp(*b*)**	**95% *CI***	**exp(*b*)**	**95% *CI***
PHQ-9 Total	**1.09***	1.03-1.15	1.05†	1.00-1.11	1.04	0.99-1.10	1.03	0.97-1.08
PHQ-9 Cognitive/affective	**1.07***	1.02-1.13	1.04	0.99-1.10	1.03	0.98-1.09	1.01	0.96-1.07
PHQ-9 Somatic	**1.10***	1.04-1.16	**1.06***	1.00-1.11	1.05†	0.99-1.11	1.04	0.98-1.09
SSRI Use					0.98	0.84-1.13	0.99	0.86-1.15
TCA Use					0.97	0.84-1.13	0.98	0.84-1.13
Other Antidepressant Use					1.14	0.97-1.33	1.15†	0.98-1.34
	HIV-Negative (*n*=843)							
PHQ-9 Total	1.02	0.96-1.07	1.01	1.00-1.02	1.00	0.94-1.06		
PHQ-9 Cognitive/affective	1.01	0.96-1.07	1.00	0.95-1.06	1.00	0.94-1.06		
PHQ-9 Somatic	1.02	0.96-1.08	1.00	0.95-1.06	1.00	0.94-1.06		
SSRI Use					1.09	0.92-1.29		
TCA Use					0.97	0.83-1.15		
Other Antidepressant Use					0.95	0.81-1.13		

Note. D-dimer is log transformed. PHQ-9 variables are *z* scored. Statistically significant effects are bolded. HIV = human immunodeficiency virus. VACS = Veterans Aging Cohort Study. exp(b) = exponentiated regression coefficient. CI = confidence interval. PHQ-9 = Patient Health Questionnaire-9. SSRI = selective serotonin reuptake inhibitor. TCA = tricyclic antidepressant.

[a]Adjusted for age, sex, and race/ethnicity.

[b]Additionally adjusted for cardiovascular disease, diabetes, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, statin use, hepatitis C infection, renal function, hemoglobin, BMI, smoking, alcohol use, and cocaine abuse/dependence.

[c]Additionally adjusted for CD4+ T-cell count, HIV-1 RNA level, and ART use.

*$p < .05$

†$p = .05$-$.10$

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